1458

Cephalon
deliver more

Cephalon, Inc.
41 Moores Road
Frazer, PA 19355
Ph 610-738-6465
Fx 610-727-7651
cvocik@cephalon.com

OIPE IAP44
MAY 07 2007
PATENT & TRADEMARK OFFICE

May 7, 2007

HAND-DELIVERED

Commissioner of Patents and Trademarks
Mail Stop: Hatch-Waxman PTE
Washington, D.C. 20231

Re: Application for Extension of Patent Term
Patent No. 4,927,855
Issued: May 22, 1990
Title: **Levorotatory Isomer of Benzhydrylsulfinyl Derivatives**
Inventor(s): Louis Lafon
Assignee: Laboratoire L. Lafon
Agent: Cephalon, Inc.
Attorney Docket No.: CP265

Sir:

Three (3) copies of the following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Application for Interim Extension of Patent Term Based on Ongoing Regulatory Review of a New Drug Application as Provided Under 35 U.S.C. § 156(E)(2) (in triplicate);

2. Exhibits A through D;

3. Check no. 12591 in the amount of $420 representing the filing fee for this application; and

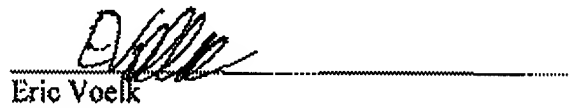
4. One (1) return postcard.

It is respectfully requested that the enclosed postcard be stamped with the date the enclosed documents are received by the PTO and that it be returned as soon as possible.

05/07/2007 [illegible]
01 FC:[illegible]

The Commissioner is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 03-1195. A duplicate copy of this letter is enclosed.

Respectfully requested



Eric Voelk
Cephalon, Inc.
Registration No. 45,185

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent 4,927,855
Issued:	May 22, 1990
Inventor:	Louis Lafon
Assignee:	Laboratoire L. Lafon
Agent:	Cephalon, Inc.
For:	**Levorotatory Isomer of Benzhydrylsulfinyl Derivatives**

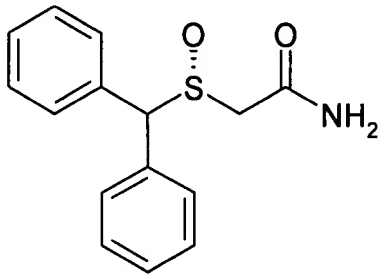
Commissioner of Patents and Trademarks
Mail Stop: Hatch-Waxman PTE
Washington, D.C. 20231

APPLICATION FOR INTERIM EXTENSION OF PATENT TERM BASED ON AN ONGOING REGULATORY REVIEW OF A NEW DRUG APPLICATION AS PROVIDED UNDER 35 U.S.C. § 156(e)(2)

Sir:

Applicant Cephalon, Inc., ("Cephalon") owner and holder of a New Drug Application ("NDA") pending approval, hereby makes application under 35 U.S.C. § 156(d)(5) and § 156(e)(2) and 37 C.F.R. § 1.790 for interim extension of the term of U.S. patent 4,927,855 issued on May 22, 1990. The current expiration date of this patent is May 22, 2007. Applicant reasonably believes its NDA approval will occur after May 22, 2007. The interim extension requested is for a period of one year, or such greater or lesser period as the Commissioner may deem the applicant to be entitled. The extended expiration date of the patent based on this first interim extension period would be May 22, 2008. This is shorter in duration than the maximum period of extension to which the applicant would be entitled in the event of NDA approval. With respect to the applicant Cephalon's NDA, the Food and Drug Administration ("FDA") has issued an "Approvable Letter," pursuant to which the applicant has now concluded that such NDA will not be approved by the FDA prior to the May 22, 2007 patent expiration date. This pending NDA seeks approval for a human drug, whose active ingredient is claimed in U.S. patent 4,927,855. Accordingly, the NDA approval being sought is for the subject of such patent. This extension is being sought during the period beginning six months and ending 15 days before the term of such patent is due to expire. This six-month/15 day period began on November 22, 2006 and will end on May 7, 2007.

This application for extension is based on the filing for regulatory approval of the new drug NUVIGIL™ (armodafinil) Tablets under the provisions of section 505(b) of the Food, Drug and Cosmetic Act. The sole active ingredient in NUVIGIL is armodafinil or 2-[(R)-(diphenylmethyl)sulfinyl]acetamide, a compound of the formula:



The active ingredient in NUVIGIL Tablets, methods of using the active ingredient, and the active ingredient in the form of a pharmaceutical composition for human drug use are claimed in the patent. Applicant believes that the NDA approval for NUVIGIL Tablets will be the first permitted commercial marketing or use of this active ingredient in the United States. The active ingredient in NUVIGIL is the isolated and purified levorotatory enantiomer of the active racemic ingredient in the previously approved drug product PROVIGIL®.

The assignee of the entire right, title and interest in U.S. patent 4,927,855 is Laboratoire L. Lafon by virtue of an assignment from the inventor Louis Lafon and such patent was issued by the U.S. Patent and Trademark office in the name of the aforementioned assignee. Laboratoire L. Lafon has changed its name to Cephalon France, as documented in **Exhibit A**. Applicant Cephalon, Inc. is the holder and owner of the aforementioned NDA for NUVIGIL Tablets and is making this application as the duly authorized agent of the assignee, for and in the name of the assignee. Attached as **Exhibit B** is a letter of appointment of agent from the assignee.

In accordance with the provisions of 37 C.F.R. § 1.790 (incorporating by reference certain provisions of 37 C.F.R. § 1.740), applicant provides the following information:

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

Applicant submits that the appropriate chemical and generic name for the active ingredient in NUVIGIL Tablets has been set forth above. Otherwise, armodafinil is an enantiomeric compound with a molecular weight is 273.35 and is typically prepared as a white to off-white, crystalline powder that is very slightly soluble in water, sparingly soluble in acetone and soluble in methanol.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The approval for NUVIGIL Tablets is being sought at the Food and Drug Administration pursuant to the regulatory review provisions of section 505(b) of the Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory period occurred.

This information is not required in connection with an application for interim extension. Applicant Cephalon, Inc. has, however, received letters from the FDA dated April 28, 2006 and December 22, 2006 indicating that the NDA seeking approval to market NUVIGIL Tablets is approvable, but such approval has not taken place and may not take place prior to May 22, 2007, based on the applicant's reasonable belief as to the time required to complete compliance with outstanding regulatory requirements.

(4) An identification of each active ingredient in the product and a statement that each such active ingredient has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in NUVIGIL Tablets has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act. The active ingredient in NUVIGIL is the isolated and purified levorotatory enantiomer of the active racemic ingredient in the drug product PROVIGIL, which has been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act.

(5) A statement that the application is being submitted within the sixty-day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

This information is not required in connection with an application for interim extension. This application is otherwise being submitted in a timely manner, as noted above. In particular, this application is being submitted prior to the end of the 15 day pre-expiration period ending on May 7, 2007 but not earlier than the start of the six-month period on November 22, 2006.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

This application for extension relates to U.S. patent 4,927,855 issued on May 22, 1990 on a non-provisional application filed January 28, 1987 (claiming priority to a French patent application no. 86 01337 filed January 31, 1986), of Louis Lafon, set to expire on May 22, 2007, seventeen years from the U.S. patent issue date. This patent is assigned to Laboratoire L. Lafon (now known as Cephalon France), with respect to which the applicant is its agent for the purpose of seeking extension. Attached as **Exhibit B** is a letter of appointment of agent from the assignee.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the patent for which an extension is being sought, including the entire specification (including claims) appears in **Exhibit C.**

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

The patent for which extension is being sought has not been the subject of an disclaimer, certificate of correction, or reexamination certificate. Maintenance fee payments have been made on October, 25, 1993, November 24, 1997 and October 22, 2001, receipts of which are enclosed as **Exhibit D**.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the product.

The approved product is the active ingredient in NUVIGIL Tablets, armodafinil or 2-[(R)-(diphenylmethyl)sulfinyl]acetamide. The patent claims 1, 2 and 4-6 are directed to the approved product or a method of using the approved product or the approved product in the form of a pharmaceutical composition.

Patent Claim	*Relationship with Approved Product*
1. (-)-Benzhydrylsulfinylacetamide.	The active ingredient in proposed product is 2-[(R)-(diphenylmethyl)sulfinyl]acetamide, which has the same chemical name as (-)-Benzhydrylsulfinylacetamide.
2. A method for the treatment of hypersomnia, which comprises administering, to a patient in need of such a treatment, an effective amount of a pharmaceutical composition consisting essentially of (-)-benzhydrylsulfinylacetamide as an arousing agent.	The proposed indications for approval (excessive sleepiness with obstructive sleep apnea/hypopnea syndrome, narcolepsy, and shift work sleep disorder) are subclasses of hypersomnia.
4. A therapeutic composition comprising an amount (-)-benzhydrylsulfinylacetamide in combination with a physiologically acceptable excipient effective to serve as an arousing agent.	The proposed product, in the form of a therapeutic composition, is the subject of this claim. Refer to the characterization of claim 1 above.
5. A therapeutic composition comprising an amount effective as a central nervous system stimulant of (-)-benzhydrylsulfinylacetamide in combination with a physiologically acceptable excipient.	The proposed product, in the form of a therapeutic composition, is the subject of this claim. Refer to the characterization of claim 1 above.
6. A pharmaceutical composition useful in therapy as a central nervous system stimulant consisting essentially of (-)-benzhydrylsulfinylacetamide in combination with a physiologically acceptable medium.	The proposed product, in the form of a therapeutic composition, is the subject of this claim. Refer to the characterization of claim 1 above.

(10) **A statement beginning on an new page, of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period, particularly, for a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and date on which the NDA was approved or the Product License issued.**

For the NDA Approval of NUVIGIL Tablets the following are the applicable dates:

Effective date for IND	October 31, 2003
IND No.	68,517
Initial Submission of NDA	March 31, 2005
NDA No.	21-875
NDA Approval for NDA	reasonably believed to be after May 22, 2007

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

A brief description of significant activities undertaken by Cephalon, Inc. during the regulatory review period for NUVIGIL, together with applicable dates for such activities, are the following:

1. Between May 2003 and July 2006, Cephalon conducted at least 15 clinical studies.

2. The clinical development program included 6 studies of pharmacokinetics and pharmacodynamics, 5 multi-center randomized, double-blind, placebo-controlled parallel-group Phase 3 studies and 3 multicenter open-label, flexible-dosage Phase 3 studies.

3. Key regulatory and clinical study dates are as follows:

Key Regulatory Dates:

October 31, 2003	IND 68,517 submission to FDA
November 26, 2003	Clearance from FDA to proceed with clinical studies
October 22, 2004	Pre-NDA Meeting
March 31, 2005	NDA 21-875 submission
April 7, 2005	FDA acknowledged receipt of NDA
June 10, 2005	Provided FDA Reviewer's Aid
July 18, 2005	Response to FDA Request
August 19, 2005	Response to FDA Request
October 31, 2005	Response to FDA Request
January 30, 2006	FDA action date extension letter
February 10, 2006	Response to FDA Request
April 6, 2006	Response to FDA Request
June 30, 2006	Response to approvable letter
August 15, 2006	Type II DMF Original Submission for armodafinil
December 19, 2006	Response to FDA Request
December 22, 2006	FDA action date extension letter
February 23, 2007	Response to FDA Request
March 16, 2007	Response to FDA Request
April 16, 2007	Response to approvable letter

Key Clinical Study Dates:

May-June 2003	Study 101 (PK/tolerance)
June – Sept. 2003	Study 102 (PK/tolerance)
June – Sept. 2003	Study 103 (PK/PD)
May 2004	Study 1021 (extrinsic PK)
June – July 2004	Study 1022 (extrinsic PK)

July 2004	Study 1023 (bioequivalence)
Oct. – Dec. 2004	Study 1025 (extrinsic PK)
March 2004 – Jan 2005	Study 3020 (Phase 3: safety/efficacy)
Feb. – Nov. 2004	Study 3021 (Phase 3: safety/efficacy)
April – Dec. 2004	Study 3022 (Phase 3: safety/efficacy)
March – Oct. 2004	Study 3025 (Phase 3: safety/efficacy)
Feb. 2004 – July 2006	Study 3023 (Phase 3: safety/efficacy)
Feb. 2004 – July 2006	Study 3024 (Phase 3: safety/efficacy)
Sept. – Dec. 2005	Study 3045 (Phase 3: safety/efficacy)
Oct. 2004 – July 2006	Study 3046 (Phase 3: safety/efficacy)

4. Additional information related to the NDA was submitted by Cephalon to the FDA on the following dates:

June 7, 2005	January 12, 2006	January 22, 2007
June 10, 2005	January 25, 2006	February 7, 2007
June 13, 2005	January 27, 2006	February 13, 2007
June 24, 2005	February 10, 2006	February 14, 2007
August 12, 2005	March 24, 2006	February 23, 2007
August 19, 2005	April 5, 2006	February 27, 2007
September 27, 2005	April 6, 2006	March 16, 2007
September 29, 2005	June 30, 2006	March 20, 2007
October 28, 2005	August 11, 2006	March 29, 2007
October 31, 2005	November 13, 2006	April 16, 2007
December 16, 2005	December 19, 2006	

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

Applicant believes that it will, in the event of an NDA approval, be entitled to an extension for U.S. patent 4,927,855 in accordance with the provisions of 35 U.S.C. § 156. Applicant believes that the period of extension applicable to the patent will then be greater than 1042 days, based on an NDA approval that it is reasonably believed will occur *after May 22, 2007.* An NDA approval on May 22, 2007 would provide the following:

	Patent Information:
Patent Issue Date	May 22, 1990
Non-Provisional U.S. Patent Priority Date	January 28, 1987
	FDA Information:
Date IND Becomes Effective	October 31, 2003
Date NDA Submitted to the FDA	March 31, 2005
Date NDA Approved by the FDA	May 22, 2007
	IND Period:
Start Date of Regulatory Review Period	October 31, 2003
IND Review Period (days)	518
½ IND Review Period (days)	259
	Reg. Rev. Period Allowed:
NDA Review Period (days)	***783***
Regulatory Review Period	1301
Reg. Review Period Less ½ IND Period (days)	1042
	Statutory Limitations:
Patent Expiration Date (>17 or 20 year term)	*May 22, 2007*
Expiration Under 5 Year Limitation Period	May 22, 2012
Expiration of 14 years from NDA Approval	May 22, 2021
Expiration Based on Regulatory Review Period	March 29, 2010
Maximum Extension Based on All Limitations:	***March 29, 2010***
Maximum Extension in Days:	1042

Applicant, therefore, believes that it is entitled to the one-year interim extension being sought in this application based in part on the substantially greater term of extension to which applicant will be entitled in the event the NDA is approved.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see 37 C.F.R. § 1.765).

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (see 37 C.F.R. § 1.20(j)).

Applicant hereby encloses a check in the amount of the prescribed fee under 37 C.F.R. § 1.20(j)(2), $420.00 for an initial application for interim extension. If for any reason this payment is insufficient, applicant hereby authorizes that any deficiency may be charged to Deposit Account No. 03-1195.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Please direct all correspondence in connection with this application to:

Robert T. Hrubiec, Ph.D., J.D.
Vice President, Intellectual Property & Chief Patent Counsel
Cephalon, Inc.
41 Moores Road
PO Box 4011
Frazer, PA 19300

(16) A duplicate of the application papers, certified as such.

Applicant hereby certifies that this application is accompanied by 2 additional copies.

(17) An oath or declaration.

Applicant, through its undersigned patent attorney authorized to practice before the Patent and Trademark Office and who has general authority from the agent or owner to act on behalf of the agent or owner in patent matters, being duly warned that willful false statements are punishable by fine or imprisonment or both under section 1001 of Title 18, United States Code and that willful false statements and the like may jeopardize the validity of this application and the patent to which it relates, states and declares that the following statements made based on his

own knowledge are true and that all statements made on information and belief are believed to be true:

(1) The undersigned is registered to practice before the Patent and Trademark Office and is making this declaration as a patent attorney who has general authority to act on behalf of the applicant in patent matters.

(2) The undersigned has reviewed and understands the contents of the application being submitted pursuant to this section;

(3) The undersigned believes the patent is subject to an extension pursuant to 37 C.F.R. § 1.710 in the event of NDA approval and, in the interim, is subject to an extension pursuant to 37 C.F.R. § 1.790;

(4) The undersigned believes an extension of the length claimed is justified under 35 U.S.C. 156 and the applicable regulations; and

(5) The undersigned believes the patent for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720 in the event of NDA approval, and meets the requirements for an interim extension of a patent set forth in 37 C.F.R. § 1.790.

If this application for extension of patent term is held to be informal, applicant may seek to have that holding reviewed by filing a petition with the required fee, as necessary, pursuant to 37 C.F.R. §§ 1.181, 1.182 or 1.183, as appropriate, within such time as may be set in any notice that the application has been held to be informal, or if no time is set, within one month of the date on which the application was held informal.

Respectfully submitted,

CEPHALON, INC.

Date: 5-7-07

By: _____

Eric Voelk
Reg. No. 45,185
Director, Intellectual Property
Cephalon, Inc.

Attachments:
Check for $ 420.00
Exhibit A - Authorization for Changing Name of Laboratoire L. Lafon to Cephalon France
Exhibit B - Letter of appointment of agent
Exhibit C - Copy of U.S. patent 4,927,855
Exhibit D - Maintenance Fee Statements

EXHIBIT A

Authorization for Changing Name of Laboratoire L. Lafon to Cephalon France

LABORATOIRE L. LAFON
Société Anonyme au capital de € 11.553.920
Siège Social : 19, avenue du Professeur Cadiot 94700 Maisons-Alfort
552 061 962 RCS Créteil

PROCES-VERBAL DES DELIBERATIONS DE L'ASSEMBLEE GENERALE EXTRAORDINAIRE DU 12 FEVRIER 2003

L'an 2003,

Le mercredi 12 février,

A 14 heures,

Les actionnaires de la société LABORATOIRE L. LAFON, société anonyme au capital de € 11.553.920, divisé en 18.053 actions de € 640 chacune, dont le siège est 19, avenue du Professeur Cadiot, 94700 Maisons-Alfort, se sont réunis en Assemblée Générale Extraordinaire, au 20, rue Charles Martigny, 94700 Maisons-Alfort, sur convocation faite par le Conseil d'Administration selon lettre simple adressée à chaque actionnaire.

Il a été établi une feuille de présence, qui a été émargée par chaque membre de l'Assemblée en entrant en séance, tant en son nom qu'en qualité de mandataire.

L'Assemblée est présidée par Monsieur Alain Aragues, en sa qualité de Président du Conseil d'Administration.

Organisation de Synthèse Mondiale Orsymonde, représentée par Monsieur Alain Aragues, seul autre actionnaire présent et acceptant cette fonction, est appelée comme scrutateur unique.

Madame Ann Baugas est désignée comme secrétaire.

Monsieur Albert Rojtman, Commissaire aux Comptes titulaire, régulièrement convoqué par lettre recommandée avec demande d'avis de réception, est absent

Les membres du Comité d'Entreprise qui assistent à l'Assemblée sont :

Madame Elizabeth Jean

La feuille de présence, certifiée exacte par les membres du bureau, permet de constater que les actionnaires présents, représentés ou ayant voté par correspondance possèdent 18.050 actions sur les 18.053 actions ayant le droit de vote.

En conséquence, l'Assemblée, réunissant plus que le quorum requis par la loi, est régulièrement constituée et peut valablement délibérer.

Le Président dépose sur le bureau et met à la disposition des membres de l'Assemblée :

- les copies des lettres de convocation adressées aux actionnaires ;
- la copie et l'avis de réception de la lettre de convocation du Commissaire aux Comptes ;
- les copies des lettres de convocation adressées aux représentants du Comité d'Entreprise ;
- la feuille de présence et la liste des actionnaires ;
- un exemplaire des statuts de la Société ;
- le rapport du Conseil d'Administration ;
- le texte du projet des résolutions qui sont soumises à l'Assemblée.

Le Président déclare que les documents et renseignements prévus par les dispositions législatives et réglementaires ont été adressés aux actionnaires ou tenus à leur disposition au siège social pendant le délai fixé par lesdites dispositions.

L'Assemblée lui donne acte de cette déclaration.

Le Président rappelle que l'Assemblée est appelée à délibérer sur l'ordre du jour suivant :

ORDRE DU JOUR

- Lecture du rapport du Conseil d'Administration ;
- Modification de la dénomination sociale ;
- Transfert du siège social ;
- Modification corrélative des statuts ;
- Pouvoirs pour l'accomplissement des formalités.

Il est ensuite donné lecture du rapport du Conseil d'Administration.

Puis, le Président déclare la discussion ouverte.

Personne ne demandant la parole, le Président met successivement aux voix les résolutions suivantes :

PREMIERE RESOLUTION

L'Assemblée Générale, après avoir entendu la lecture du rapport du Conseil d'Administration, décide qu'à compter de ce jour, la dénomination sociale sera "CEPHALON FRANCE" au lieu de "LABORATOIRE L. LAFON".

Cette résolution est adoptée à l'unanimité.

DEUXIEME RESOLUTION

L'Assemblée Générale, après avoir entendu la lecture du rapport du Conseil d'Administration, décide de transférer le siège social du 19, avenue du Professeur Cadiot, 94700 Maisons-Alfort au 20, rue Charles Martigny, 94700 Maisons-Alfort, et ce à compter de ce jour.

Cette résolution est adoptée à l'unanimité.

TROISIEME RESOLUTION

En conséquence de l'adoption des résolutions précédentes, l'Assemblée Générale décide de modifier les articles 3 et 4 des statuts de la Société dont la rédaction est désormais la suivante :

ARTICLE 3 - Dénomination

"La dénomination de la Société est : CEPHALON FRANCE."

Le reste de l'article demeure inchangé.

ARTICLE 4 - Siège social

"Le siège social est fixé au : 20, rue Charles Martigny, 94700 Maisons-Alfort."

Le reste de l'article demeure inchangé.

Cette résolution est adoptée à l'unanimité.

QUATRIEME RESOLUTION

L'Assemblée Générale donne tous pouvoirs au porteur de copies ou d'extraits du présent procès-verbal pour remplir toutes formalités de droit.

Cette résolution est adoptée à l'unanimité.

L'ordre du jour étant épuisé et personne ne demandant plus la parole, le Président déclare la séance levée.

De tout ce que dessus, il a été dressé le présent procès-verbal qui, après lecture, a été signé par les membres du bureau.

Le Président

Le Scrutateur unique

Le Secrétaire

42622.1.10

Certifié Conforme

EXHIBIT B

Letter of appointment of agent

AUTHORIZATION AND POWER OF ATTORNEY

May 7, 2007

Cephalon, Inc.
Attention: Robert T. Hrubiec, Vice President, Intellectual Property and Chief Patent Counsel
41 Moores Road
Frazer, PA 19380

Re: U.S. Patent 4,927,855

Dear Dr. Hrubiec:

Laboratoire L. Lafon, a corporation organized under the laws of France and assignee of the entire right, title and interest in U.S. Patent 4,927,855, hereby appoints Cephalon, Inc. as its agent under 35 U.S.C. 156(d)(1) and 156(d)(5)(c) to seek patent term extensions, including interim extensions, of the aforementioned U.S. Patent 4,927,855 with full authority to apply for and to receive any such extension for and on behalf of Laboratoire L. Lafon.

Respectfully submitted,

LABORATOIRE L. LAFON

By: _____
Name: Robert P. Roche, Jr.
Title: Director

EXHIBIT C

Copy of U.S. patent no. 4,927,855

United States Patent [19]

Lafon

[11] **Patent Number: 4,927,855**

[45] **Date of Patent: May 22, 1990**

[54] **LEVOROTATORY ISOMER OF BENZHYDRYLSULFINYL DERIVATIVES**

[75] Inventor: **Louis Lafon**, Paris, France

[73] Assignee: **Laboratoire L. Lafon**, Maisons Alfort, France

[21] Appl. No.: **7,720**

[22] Filed: **Jan. 28, 1987**

[30] **Foreign Application Priority Data**

Jan. 31, 1986 [FR] France 86 01337

[51] **Int. Cl.**[5] **A61K 31/165**; C07C 147/14; C07C 103.22

[52] **U.S. Cl.** **514/618**; 514/133; 514/139; 514/162; 562/430; 560/11; 560/15

[58] **Field of Search** 564/162, 133, 139; 514/618

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,177,290 12/1979 Lafon 514/618

FOREIGN PATENT DOCUMENTS

0097071 12/1983 European Pat. Off. 564/162

Primary Examiner—Floyd D. Higel
Attorney, Agent, or Firm—Kuhn and Muller

[57] **ABSTRACT**

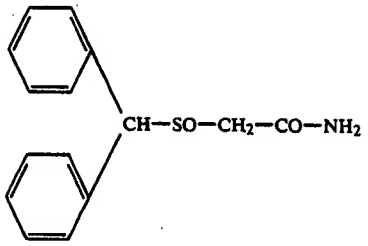
The levorotatory isomer of benzhydrylsulfinylacetamide has useful pharmaceutical activity on the central nervous system, particularly as an antidepressant and stimulant in the treatment of hypersomnia and Alzheimer's disease.

6 Claims, No Drawings

LEVOROTATORY ISOMER OF BENZHYDRYLSULFINYL DERIVATIVES

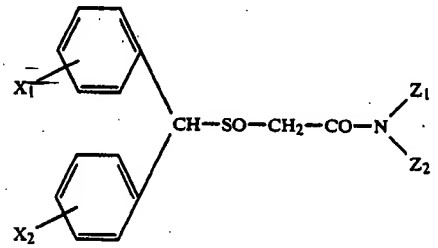
The present invention relates to the levorotatory derivative of benzhydrylsulfinylacetamide, the method for its preparation and its use in therapy, especially as an antidepressant and stimulant for the central nervous system (CNS), the said derivative being useful in particular in the treatment of hypersomnia on account of its arousing effects.

It is known that French Pat. No. 78 05 510 (publication No. Fr-B-2 385 693) describes the racemate (±)-benzhydrylsulfinylacetamide, which has the code number CRL 40 476 and the following structural formula:



as a product (see Example 1 of the said French patent) and as stimulant for the central nervous system (CNS).

It is also known that, in Patent Document EP-A-No. 0 097 071, the neuropsychopharmacological properties of the racemate were compared with those of the analogs of the formula:



in which:

X_1 and X_2, which can be identical or different, each represent, H, Cl or F,

Z_1 represents CH_3, CH_2Ch_3, $CH(CH_3)_3$, it also being possible for Z_1 to represent a hydrogen atom when at least one of the symbols X_1 and X_2 is different from H, and

Z_2 represents H, it being possible for NZ_1Z_2, considered together, to represent a piperidino or morpholino group,

which act on the CNS as sedatives in some cases and as stimulants in others (see especially Table I on page 3 and Table IV on page 4 of the said European patent document).

It has now been found that the levorotatory compound (−)-benzhydrylsulfinylacetamide (Code no.: CRL 40 982) has valuable therapeutic properties compared with the racemate (±)-benzhydrylsulfinylacetamide (Code no.: CRL 40 476) and with the dextrorotatory compound (+)-benzhydrylsulfinylacetamide (Code no.: CRL 40 983). Surprisingly, it has been found that the metabolism of the levorotatory compound in the organism is different form that of the racemate and the dextrorotatory compound and that the levorotatory compound is particularly valuable in the treatment of hypersomnia and Alzheimer's disease.

According to the invention, a novel industrial product is recommended which is useful in therapy and belongs to the family of the benzylhydrylsulfinyl derivatives, the said product being (−)-benzhydrylsulfinylacetamide.

This levorotatory compound cannot be prepared by isolation from the corresponding racemic amide. However, it can be prepared by chemical synthesis from a precursor of the amide, according to a method known per se, by the application of conventional reaction mechanisms.

The method of preparation recommended according to the invention consists in:

(1°) reacting (±)-benzhydrylsulfinylacetic acid with (−)-α-methylbenzylamine to give the (−)-benzhydrylsulfinylacetate of (−)-α-methylbenzylamine (the reaction advantageously being carried out in the presence of a small excess of amine relative to the stoichiometric conditions, and more particularly with a molar ratio amine/acid of between 1.02/1 and 1/15/1 and preferably of between 1.05/1 and 1.10/1),

(2°) converting the resulting (−)-benzhydrylsulfinylacetate salt of (−)-α-methylbenzylamine to (−)-benzhydrylsulfinylacetic acid [the conversion advantageously being carried out by hydrolysis in an acid medium, the solvent being warm water (especially water at 30°–45° C.], and

(3°) subjecting the resulting (−)-benzhydrylsulfinylacetic acid to an amidation reaction with gaseous ammonia.

The amidation of stage (3°) is advantageously carried out in 2 steps, namely:

(3a) esterification of the (−)-benzhydrylsulfinylacetic acid to a lower alkyl (−)-benzyldrylsulfinylacetate [the lower alkyl being C_1–C_3, especially isopropyl, ethyl or methyl (preferably ethyl and particularly preferably methyl)], followed by

(3b) transamidation of the resulting lower alkyl (−)-benzhydrylsulfinlacetate with NH_3 (the transamidation reaction preferably being carried out in a lower alcohol and particularly preferably in the alcohol corresponding to the alkyl group of the ester obtained in stage 3a), a stream of NH_3 being passed into the reaction medium).

(±)-Benzyhydrylsulfinylacetic acid is a known substance which is described as synthesis intermediate in Patent Document FR-B-No. 2 326 181 (m.p. (inst.)= 16-4°–165° C.).

According to the invention, a therapeutic composition is recommended which contains (−)-benzhydrylsulfinylacetamide as the active ingredient, in association with a physiologically acceptable excipient. Of course, in a composition of this type, the said (−)-benzhydrylsulfinylacetamide is present in a pharmaceutically effective amount.

It is also recommended to use this levorotatory compound to obtain, on the one hand, an arousing drug to be used in human therapy for hypersomnia, and, on the other hand, a stimulating drug, and in particular a drug for inhibiting aphasia and ideomotor apraxia, to be used in therapy for Alzheimer's disease.

Further advantages and characteristics of the invention will be understood more clearly from the following

description of (i) preparation examples and (ii) results of comparative neurophyschopharmacological tests. These data, which in no way imply a limitation, are given by way of illustration.

PREPARATION I

Preparation of (−)-benzhydrylsulfinylacetamide

(Example 1; Code no.: CRL 40 982)

(a) (−)-Benzhydrylsulfinylacetate of (−)-α-methylbenzylamine

13 g (0.108 mol) of (−)-α-methylbenzylamine are added to a suspension of 27.4 g (0.1 mol) of (±)-benzhydrylsulfinylacetic acid (m.p. (inst.)=164°-165° C.; Code no.: CRL 40 467) in 500 ml of water; the mixture is filtered hot, the filtrate is cooled and the product is filtered off and recrystallized twice from 300 ml of water to give 17 g (yield: 42%) of the (−)-benzhydrylsulfinylacetate of (−)-α-methylbenzylamine. M.p. (inst.)=148°-150° C.

(b) (−)-Benzhydrylsulfinylacetic acid

the (−)-benzhydrylsulfinylacetate of (−)-α-methylbenzylamine (17 g) obtained in this way is dissolved in 800 ml of warm water (30°-40° C.) and then acidified with 7 ml of concentrated hydrochloric acid (12N HCl, d=1.19 g/cm³). The mixture is filtered cold and the precipitate is washed with water and dried to give the expected (−)-benzhydrylsulfinylacetic acid with a yield of about 100%.

M.p. (inst.)=185°-188° C.

$\alpha_D^{20°\,C.}$ = −35° (in a 1% solution in CH_3OH).

(c) Methyl (−)-benzhydrylsulfinylacetate

A suspension of 16.45 g (0.06 mol) of (−)-benzhydrylsulfinylacetic acid in 300 ml of water is treated at 20° C. with 16.8 g (0.2 mol) of sodium bicarbonate and 18.8 ml (0.21 mol) of methyls sulfate, with stirring, the mixture is stirred for 16 to 18 hours at 20° C. and filtered and the material on the filter is washed with water and dried to give methyl (−)-benzhydrylsulfinylacetate with a yield of 85%.

M.p. (inst.)=109°-110° C.

$\alpha_D^{20°\,C.}$ = −22.5° (in a 4% solution in CH_3OH).

(d) CRL 40 982

A dry stream of NH_3 gas is passed at room temperature into a solution of 100 ml of methanol containing 8.6 g (0.03 mol) of methyl (−)-benzhydrylsulfinylacetate. NH_3 introduced in this way is reacted with the solution for 5 h, with stirring. The methanol is evaporated off, the evaporation residue is taken up in ether and the product is filtered off and recrystallized from ethanol to give CRL 40 982 with an overall yield of 32%. This product is in the form of white crystals which are soluble in alcohols and acetone and insoluble in water and ether.

M.p. (inst.)=153°-154° C.

$\alpha_D^{20°\,C.}$ = −20° (in a 2% solution in CH_3OH),

PREPARATION II

Preparation of (+)-benzhydrylsulfinylacetamide

(Comparison product CP1; Code no.: CRL 40 983)

The following are obtained successively using the procedure indicated in Preparation I above but replacing the (−)-α-methylbenzylamine with (+)-α-methylbenzylamine.

(a) the (+)-benzhydrylsulfinylacetate of (+)-α-methylbenzylamine;

M.p. (inst.)=148°-150 C.;

(b) (+)-benzhydrylsulfinylacetic acid;

M.p. (inst.)=190°-191° C.,

$\alpha_D^{20°\,C.}$ = +45° (in a 1% solution in CH_3OH);

(c) methyl (+)-benzylhydrylsulfinylacetate;

M.p. (inst.)=109°-110° C.,

$\alpha_D^{20°\,C.}$ = +22.2° (in a 4% solution in CH_3OH);

and then

(d) CRL 40 983;

M.p. (inst.)=153°-154° C.,

$\alpha_D^{20°\,C.}$ = +22° (in a 2% solution in CH_3OH).

The comparative tests which were undertaken with the levorotatory derivative according to the invention (Ex. 1; Code no.: CRL 40 982), the dextrorotatory derivative (CP1; Code no.: CRL 40 983) and the corresponding racemate (CP2; Code no.: CRL 40 476) have been summarized below. Unless indicated otherwise, the 3 products studied in these tests were administered intraperitoneally as a suspension in an aqueous solution of gum arabic, in a volume of 20 ml/kg to male mice and in a volume of 5 ml/kg to male rats.

A—TOXICITY

In male mice, the LD_O (maximum non-lethal dose) by intraperitoneal administration is found to be greater than or equal to 512 mg/kg for the dextrorotatory compound and the racemate, whereas the LD_{30} of the levorotatory compound is of the order of about 512 mg/kg.

In summary, CRL 40 982 is more toxic than CRL 40 983 (CP1) and CRL 40 476 (CP2). The fact that the toxicity of CRL 40 982 is greater than that of the other two products does not present a problem since the levorotatory compound still has a sufficiently wide useful range of non-lethal concentrations. Here, the fact that CRL 40 982 is more toxic than the other two products indicates that it is more active.

B—BEHAVIOR IN RATS

In male mice, CRL 40 982, CRL 40 983 and CRL 40 476 have stimulant effects; in male rats, on the other hand, it is found that CRL 40 982 and CRL 40 983 do not have stimulant effects while the racemate (CRL 40 476) (i) is a stimulant and (ii) has a mydriatic action at all the doses used, the levorotatory and dextrorotatory isomers being devoid of this mydriatic action when administered on their own:

at a dose of 128 mg/kg, CRL 40 476 causes excitation with an increase in the fear ration for 2 h, exophthalmos for 1 h and mydriasis for 1 for 2 h;

at a dose of 32 mg/kg, CRL 40 476 causes excitation (transient, lasting 0.5 h) with an increase in the fear reaction for 1 h, exophthalmos for 0.5-1 h and mydriasis for 1-2 h;

at a dose of 8 mg/kg, CRL 40 476 causes exophthalmos for 0.5-1 h and mydriasis for 0.5 h;

at a dose of 2 mg/kg, CRL 40 476 induces transient mydriasis appearing 1 h after administration, whereas at a doses of 64 mg/kg, 16 mg/kg, 4 mg/kg and 1 mg/kg, CRL 40 982 and CRL 40 983 cause behavior, reactivities and variations in the rectal temperature and pupil diameter which are substantially comparable to those of the control group.

C—MOTOR ACTIVITY IN MICE

The mice (6 per dose, 18 control animals) receive CRL 40 476, CRL 40 982 or CRL 40 983 four hours before being placed in an actimeter, where their motility is recorded for 30 minutes. It is found that, at doses of 128 mg/kg and to a lesser extent 64 mg/kg, the three substances used cause an increase in the motor activity four hours after their administration. However, the hyperactivity induced by CRL 40 982 and CRL 40 983

reaches a level and a degree of statistical significance which are greater than those due to CRL 40 476, especially at the highest dose used (128 mg/kg).

In summary, under the experimental conditions (intraperitoneal administration of the substances four hours before the test), CRL 40 982 shows a stimulant effect equal in intensity to that observed with CRL 40 983, while the hyperactivity induced by CRL 40 476 is less than that obtained with either CRL 40 982 or CRL 40 983.

D—PHARMACOKINETIC STUDY

In the organism, CRL 40 476 is partially converted to (±)-benzhydrylsulfinylacetic acid (CRL 40 467) of the structural formula:

$$(C_6H_5)_2CH—SO—CH_2—COOH$$

which is used as the starting material for the synthesis of the optical isomers CRL 40 982 and CRL 40 983.

Now, this metabolite is found to be inactive. In fact, CRL 40 467, administered intraperitoneally to male mice at doses of 1024 mg/kg, 512 mg/kg, 256 mg/kg, 128 mg/kg and 64 mg/kg, induces the appearance of brief sedation (with a duration less than or equal to about 50–60 minutes) and does not cause the death of any of the animals treated. Its neuropsychopharmacological study did not reveal any psychotropic activity.

to distinguish CRL 40 982 from the racemic and dextrorotatory compounds, a kinetic study of the metabolism was undertaken on dogs (group of four animals). In a randomized crossover procedure, each animal received the following at the rate of one oral administration per week: 2 administrations of CRL 40 476 (for assessment of the variations within individuals), 1 administration of CRL 40 982 and 1 administration of CRL 40 983. Following each of these administrations, the kinetics of the CRL 40 476 and CRL 40 467 present in the plasma were determined (without looking to see whether these two products were in the racemic, levorotatory and/or dextrorotatory form, because of the difficulties associated with determining the optical rotation of each of the optical isomers in a biological medium).

The dose administered for each of the test substances CRL 40 476, CRL 40 982 and CRL 40 983 was 30 mg/kg.

After administration of CRL 40 476, the said CRL 40 476 and its metabolite, CRL 40 467, are found in the plasma.

After the administration of CRL 40 982, the following are found in the plasma: the said CRL 40 982, which will be characterized and determined as being CRL 40 476 by way of convenience, in view of what has been said above, and a metabolite which will be characterized and determined as being CRL 40 467.

Likewise, after administration of CRL 40 983, the 2 corresponding products in the plasma will be characterized and determined as being CRL 40 476 and CRL 40 467.

The curves of the plasma concentrations of the said CRL 40 476 and CRL 40 467 as a function of time are plotted from time T=2 to time T=+9 h after administration of the CRL 40 476, CRL 40 982 and CRL 40 983. The areas under the curves (AUC_o^{+9h}) are then calculated. The results obtained are recorded in Table I below. They show this:

(a) after administration of CRL 40 476 and CRL 40 983, the AUC_o^{+9h} of CRL 40 476 are not statistically different, whereas, after administration of CRL 40 982, the AUC_o^{+9h} of CRL 40 476 is approximately twice the AUC_o^{+9h} of CRL 40 476 which each result from the administration of CRL 40 476 and CRL 40 476 and CRL 40 983; and

(b) the quantity of CRL 40 467 produced after administration of CRL 40 983 is very large (83.12 $mg.l^{-1}.h$), whereas the quantity produced after administration of CRL 40 982 is very small (8.69 $mg.l^{-1}.h$).

The value of CRL 40 982 according to the invention is in the fact that only a small proportion of this product is converted to inactive CRL 40 467, whereas a very high proportion of the corresponding dextrorotatory derivative is metabolized to CRL 40 467. In summary, the levorotatory compound CRL 40 982 has a better bioavailability than the racemic compound CRL 40 476 and the dextrorotatory compound CRL 40 983, in view of the small quantity of inactive metabolite which it produces in the organism.

These pharmacokinetic results were confirmed on rabbits and mice. An immunostimulant effect was also observed in vitro for CRL 40 982.

E—CLINICAL TRIALS

In human clinical trials, it was found that the elimination half-life of CRL 40 982 is relatively long (about 10 h), making it possible to obtain good results on adults with 1 to 2 administrations per day.

In the course of the clinical trials, CRL 40 982 was found to act in the short term as a purely hypnogenic, antiarousing substance and in the long term as an arousing substance useful for hypersomnia. Furthermore, in both the short and long term, CRL 40 982 was shown to be particularly active towards the symptoms of dementia and loss of memory (especially in the elderly).

Administered once or twice a day in the form of tablets or gelatin capsules each containing 50 to 100 mg of CRL 40 982, this product has a different stimulant neuropsychopharmacological profile from that of the amphetamines and tricyclic antidepressants and is useful of depressions, hypersomia and in particular Alzheimer's disease (improvement of the symptoms of dementia, memory disorders, aphasia and ideomotor apraxia).

TABLE I

PHARMACOKINETIC STUDY ON DOGS
MEASURMENT OF THE AREAS UNDER THE CURVES (AUC_o^{+9h})

Product administered	Code no.	AUC_o^{+9h} CRL 40 476 (a)		AUC_o^{+9h} CRL 40 467 (a)	
CP2	CRL 40 476	46.76 ± 6.95	**	35.12 ± 6.93	**
Ex. 1	CRL 40 982	97.22 ± 12.58	*	8.69 ± 1.22	n.s.
CP1	CRL 40 983	50.94 ± 8.77	**	83.12 ± 21.66	*

Notes
(a) in $mg.l^{-1}.h$
* statistically significant difference ($p < 0.1$)
** statistically very significant difference ($p < 0.01$)
n.s. statistically non-significant difference

What is claimed is:

1. (−)-Benzhydrylsulfinylacetamide.

2. A method for the treatment of hypersomnia, which comprises administering, to a patient in need of such a treatment, an effective amount of a pharmaceutical composition consisting essentially of (−)-benzhydrylsulfinylacetamide as an arousing agent.

3. A method for the treatment of Alzheimer's disease, which comprises administering, to a patient in need of such a treatment, an effective amount of a pharmaceutical composition consisting essentially of (−)-benzylhydrylsulfinylacetamide as a central nervous system stimulant.

4. A therapeutic composition comprising an amount (−)-benzhydrylsulfinylacetamide in combination with a physiologically acceptable excipient effective to serve as an arousing agent.

5. A therapeutic composition comprising an amount effective as a central nervous system stimulant of (−)-benzhydrylsulfinylacetamide in combination with a physiologically acceptable excipient.

6. A pharmaceutical composition useful in therapy as a central nervous system stimulant consisting essentially of (−)-benzhydrylsulfinylacetamide in combination with a physiologically acceptable medium.

* * * * *

EXHIBIT D

Maintenance Fee Statements

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4,927,855	$3,100.00	$0.00	10/22/01	07/007,720	05/22/90	01/28/87	12	NO	FL-1006-US

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4,927,855	$2,100.00	$0.00	11/24/97	07/007,720	05/22/90	01/28/87	08	NO	FL-1006-US

PTO1-439 (Rev. 09/2006)

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4,927,855	$930.00	$0.00	10/25/93	07/007,720	05/22/90	01/28/87	04	NO	FL-1006-US